PSJ3

Exhibit 674F

Board-sponsored education/training

Twenty-eight respondents stated that their board had distributed educational materials regarding treatment of patients with pain. In most cases, these were articles in newsletters or publication of the board's pain management guidelines or rules. Others mentioned distributing press releases, white papers, and pamphlets on the subject. Many of the boards provided the same information on their website. One respondent stated that "our position statement on pain management is given to physicians when they're licensed, and they're interviewed by a board member to reinforce their knowledge of [the position statement]." Others covered appropriate prescribing for pain in mandatory orientation sessions for new physician licensees. In one state, "any new physician who applies has to take a written test based on all the board's rules, [including appropriate opioid prescribing]." Several respondents emphasized that the focus of these educational efforts was on proper documentation and follow-up of patients treated for pain, particularly for chronic pain, e.g., "The [emphasis] that our board has [stressed with] physicians is documenting their treatment plan, diagnosis, and rationale for what [they're] prescribing. That's where physicians will get into trouble. It's necessary for the patient and good for the doctor; for example, if the patient needs to change physicians, those records speak volumes"; and "We sent to physicians [in the state] ... a letter saying basically 'we don't want you to overtreat or undertreat [your] patients' pain, and if you ever have a complaint with us, this is what you need to have in your file, and if you don't have it, you'll probably be in trouble with us." One respondent questioned whether physicians were "getting the message":

> [This state] has specific legislation in this practice [chronic pain management] and how it's supposed to be done. We have shared that with physicians in our newsletter, and we give talks, but the word doesn't seem to get out. Physicians who we find are overprescribing complain that "the board's picking on me," but we're not. It's an issue of good medical practice.

Another expressed frustration with the limitations of what could be accomplished by a nonautonomous board:

> My board.... can't do a lot of things because [we're] under an umbrella agency that administers our budget and other things. We can complain but are limited in what we can do.... such as writing/distributing educational brochures and all kinds of creative things.... I work with "inside the box" type people, which you see in government agencies a lot. Creativity and innovation are not encouraged, and when you achieve them, you've had to fight hard. Everything is a struggle.

Fourteen respondents reported that their board had provided educational sessions on the treatment of patients with pain. Some were talks and presentations about pain management given at hospitals or other venues. One respondent reported: "[We've] sent staff out to give presentations and have been keeping track of those since 1999. I have a list five pages long of all the places we've gone: 137 presentations since 1998, 38 [were] pain management speeches, and 25 [were] overviews with pain management references as part of the content." Another stated: "the executive director has spoken on this.... We try to be as proactive as we can." Others mentioned full- or half-day seminars or training sessions provided by the board on pain management and proper prescribing — some were one-time sessions and others were given annually or more often. One respondent referred to a recently passed law requiring physicians in the state to take "12 hours of CME [continuing medical education] on end-of-life care and pain management" as a possible solution to the problem that "a lot of people out there are not being treated appropriately for their pain, and doctors don't recognize that." Another board was "also looking at mandatory CME in pain management for physicians."

Of the twenty-four respondents whose boards did not provide educational sessions on pain management, comments included: "this is being discussed, [but it's] available in the private sector"; "we're talking about providing CME on pain management and end-of-life hospice issues, but ... nothing has been finalized"; "we defer to Purdue and other workshops"; and "I wish we had the staff; however, there are really terrific people putting CME seminars on in the community that are excellent. There's a wealth of resources in this area, so there's no excuse for not having knowledge about pain management."

Balancing the need for appropriate treatment with preventing abuse and diversion

A few respondents thought that physicians might be hesitant to prescribe opioids to terminally ill patients out of fear that they might hasten the patient's death. One respondent said that the allegations made to the board relating to undertreatment of pain typically involved "a fundamental value system" in which physicians "have very strong feelings about not wanting to hasten a patient's death." In such cases, the board "trie[s] to assure physicians that it's within accepted practice to palliate at the end of life and this is not seen as euthanasia or physician-assisted suicide, but often physicians really struggle with that issue." Most respondents, however, felt that pain management at the end of life had seen the most improvement as far as boards being better able to distinguish adequate opioid prescribing from overprescribing, as is evident in the following comment:

> The board's in a tough spot. As soon as it goes after someone for overprescribing, the first reaction is "that's chilling treatment for pain." They duck for cover under that. But those cases are apples and oranges. Those who are diverting opioids take cash only, they deal with patients who have a criminal history, they don't keep records. There's no comparison to, for example, treating a dying cancer patient. Complete apples and oranges. It's not like someone in hospice, dealing with a patient who needs pain medications. Our board has a position statement on end of life that covers all this.

Some respondents commented on the difficulty in reconciling the changing attitudes and practice standards in pain management of recent years with the ongoing problem of drug abuse and diversion. One stated: "it's a real challenge, finding that balance between under- and overtreating pain." One pointed to the difficulty of managing pain in the fragile elderly: "what might be an appropriate dose for a young person is not for an elderly frail person who's on multiple medications." For some respondents, their job was easier when there was a clearly established upper limit for prescribing opioids, as the following comments demonstrate:

> [There's been a] tremendous change in the management of chronic pain and the attitude that there doesn't seem to be any upper limit on opioids. The attitude now is "whatever works." I have problems with that because I'm faced with figuring out whether opioids are being diverted or not, and I have suspicions that a lot of patients are conning a lot of doctors into giving them meds and don't get questioned because of this "whatever works" attitude. We will have to figure out how to counter that.... We used to sanction based on the PDR [*Physicians' Desk Reference*] limit (like 40 mg a day for oxycodone), but now that's almost never the basis of our sanctions. Patients are on 700 to 800 mg of oxycodone a day.

> The numbers we're seeing, the doses are kind of unreal at times. You have a physician who's not educated in pain management, and this might sound bad, but there is this rhetoric about serving chronic pain patients, so physicians tend to do it. Some have good hearts and don't know how to do it well; some don't have the heart but see it as a way to have a practice. But they're not following good medical practice in prescribing, they're just prescribing. They don't have consults, they don't document about what's going on — sometimes it's not even based on good pharmacology, just "oh, this is good." Underprescribing is still an issue, but there's also the issue of people being so overprescribed — we had one woman who was a school bus driver and she couldn't even move [because she was so drowsy from the pain medication].

The following respondent's comment concerns the same issue — how to balance treating valid chronic pain with protection against abuse of opioids:

> Chronic pain in my opinion is a subspecialty. Even experts don't agree [on] what to do. The problem I have is not so much with the pain specialists, but at the ... level of general practitioners and internists who end up with patients with chronic pain. Sometimes they do a good job at handling it, sometimes they don't. A lot of these doctors don't know how to say no to patients, they don't really understand what's going on. They can get into trouble if they take everything a patient says at face value. How do you know if I really have a migraine? ... It's hard. No doctor really wants to bother with the chronic pain issues. I knew a pain management specialist who said it took 3 months for her to get a feel for whether certain chronic pain patients were lying to get meds. Everyone lies. We've had physicians lie who are under investigation, and if physicians lie, you can bet patients lie.

One respondent agreed that many physicians prefer not to treat patients with chronic pain, and that it is better for them to refer such patients to a pain specialist:

> Some chronic pain patients are tough to treat and some doctors feel they don't have the time to spend with those patients. One of the things I always say is don't dabble in pain medicine. Do it right, for the sake of the patient and the doctor. It's better to refer [patients to a pain specialist] than to do it half way.

Yet, another respondent identified the problem of the lack of access to quality chronic pain treatment in pain clinics and centers:

> One of the problems is that the pain clinics are undersupported, they're short of doctors willing to practice pain medicine/anesthesiology, they can't get paid. [This causes a] population of people to seek out individual physicians, some of whom lack the skill set to treat this type of patient. It's a difficult problem. One psychiatrist opened a pain clinic, no prescribing experience before. He's gone from none to the top three OxyContin prescribers

> in the state. So, how does that happen? With virtually no records kept. People are walking in with money.

Another agreed:

> It's the standard of care to take care of people's pain just like it's the standard of care not to be duped. That shows how colossally difficult the board's job is here. When do you cross over from appropriately treating pain to hurting patients? I think people get into trouble with this because it's easy money for doctors. I think the brass ring is a pain center connected with an academic center, where they're well-trained, well-managed, look at all problems, not just pain. Patients who are marginal and might be abusers are put on contracts and they have ways to keep them from participating in diversional activity.... I'm always impressed with these pain centers ... they make it undesirable for drug-seeking individuals to [use their services.]

Several respondents commented further about the difficulty boards have distinguishing valid chronic pain from drug-seeking behavior. One stated: "With the advent of new end-of-life legislation ... physicians ... feel freer to go ahead and prescribe the pain medications that are needed. This helps a lot. Regarding chronic pain, physicians are much more cautious about that." Another acknowledged:

> It's easy if the patient is terminal. It's not so easy with intractable pain. Is this a drug-seeking patient or a patient with valid intractable pain? That's a difficult call for physicians and a difficult call for us. Maybe with time there will be more sophisticated diagnostic tools available to make it easier.

Discussion

Our study results indicate significant variation among state medical boards regarding experience with and reaction to overprescribing and underprescribing opioids for pain treatment. With respect to overprescribing, states were divided on their perceptions of whether the number of complaints, investigations, and disciplinary actions for opioid overprescribing over the past 5 years had increased, decreased, or stayed the same. The largest group, in each case, indicated they thought the numbers had stayed the same. A slightly smaller, but significant, group thought they had increased, and only a few believed they had decreased. However, it appears from the data that there was consistency in responses regarding trends in complaints, investigations, and disciplinary actions. That is, if the number of opioid overprescribing complaints was perceived to have increased in a jurisdiction, the number of investigations and disciplinary actions either increased or stayed the same. Likewise, if the number of complaints stayed the same or decreased, the number of investigations and disciplinary actions either stayed the same or decreased. These results were based on perceptions (rather than actual numbers), as it is still the case that most states lack systems that track complaints based on opioid prescribing.

We questioned whether the presence of a state prescription monitoring program might have had an influence on the number of complaints or investigations related to opioid prescribing. Compared to respondents from states without an electronic prescription monitoring program, we found that respondents from states with such a program were generally more likely to think the numbers of complaints, investigations, and disciplinary actions against physicians related to opioid prescribing had stayed the same over the past 5 years rather than increased or decreased (see Table 2). Regarding estimates of the number of opioid overprescribing and underprescribing complaints received in 2001, there were no statistically significant differences between boards with and boards without an electronic prescription monitoring program. Thus, based on respondents' estimates and perceptions, it does not appear that electronic data tracking mechanisms led to increased numbers of complaints, investigations, or disciplinary actions against physicians related to opioid overprescribing practices.

While nearly two-thirds of respondents reported that opioid overprescribing complaints had decreased or stayed the same, over a third of respondents perceived that opioid overprescribing complaints had increased in their jurisdiction during the past 5 years. This appeared tied to a perception that drug diversion, in general, had been increasing. A significant number of respondents believed that drug diversion on the whole was worse in their state than it was 5 years ago, although some attributed this to more diligent efforts to seek out such diversion. Of the eighteen respondents who thought drug diversion had worsened in their state, fifteen thought that OxyContin had significantly contributed to this problem. On the other hand, of the thirty-three respondents who had an opinion on this issue, fourteen (42 percent) did not think OxyContin was a problem in their state. This is likely due to the variation in abuse patterns of OxyContin across the nation. A large majority of respondents stated that their board had not changed its investigative approach in light of OxyContin concerns, but the overall tone of their comments regarding drug diversion indicated that, in general, their boards had taken more active steps to address this problem.

As regards decisions to investigate physicians for overprescribing, it appears that a number of boards are attempting to find the appropriate balance between identifying physicians who overprescribe and those who are appropriately

Table 2. Differences in Perceived 5-Year Trends of Complaints, Investigations, and Disciplinary Actions Against Physicians Related to Opioid Prescribing Based on the Presence or Absence of a State Prescription Monitoring Program (PMP).

	Increased		Decreased		Same		Don't Know	
	PMP*	no PMP**	PMP	no PMP	PMP	no PMP	PMP	no PMP
5-year trend of complaints for opioid overprescribing[A]	2 (18%)	12 (44.5%)	1 (9%)	3 (11%)	7 (64%)	10 (37%)	1 (9%)	2 (7.5%)
5-year trend of complaints for pain undertreatment[B]	1 (9%)	5 (18.5%)	1 (9%)	1 (4%)	9 (82%)	18 (66.5%)	0 —	3 (11%)
5-year trend of investigations for opioid overprescribing[C]	5 (45.5%)	10 (37%)	1 (9%)	2 (7.5%)	4 (36%)	13 (48%)	1 (9%)	2 (7.5%)
5-year trend of physicians disciplined for opioid overprescribing[D]	3 (27%)	11 (41%)	1 (9%)	5 (18.5%)	6 (56%)	9 (33%)	1 (9%)	2 (7.5%)

**"PMP" = state had an electronic prescription monitoring program before 2000 (n = 11).*

***"no PMP" = state did not have an electronic prescription monitoring program before 2000 (n = 27).*

A: *Respondents were asked whether they thought the number of complaints regarding physicians who allegedly prescribed opioids unnecessarily, in too high a dose, or for too long a duration ("overprescribed") had increased, decreased, or stayed the same over the past 5 years.*

B: *Respondents were asked whether they thought the number of complaints regarding physicians who undertreated or inadequately treated a patient's pain had increased, decreased, or stayed the same over the past 5 years.*

C: *Respondents were asked whether they thought the number of investigations related to opioid prescribing had increased, decreased, or stayed the same over the past 5 years. Because the number of board investigations for opioid underprescribing was so small, answers to this question were interpreted as relating to opioid overprescribing trends.*

D: *Respondents were asked whether they thought the number of physicians disciplined for opioid overprescribing had increased, decreased, or stayed the same over the past 5 years.*

treating patients with chronic pain. A number referred to the fact that their board had developed a policy or guidelines for prescribing for chronic pain that were a significant aid to them in deciding whether to investigate or discipline a physician. The number of boards that have adopted pain management guidelines, regulations, or policies has, in fact, increased over the last 4 years, with boards specifically addressing the issue of chronic nonmalignant (or "intractable") pain. In 2001, the PPSG documented a total of eighty-two state pain policies in the form of statutes, regulations, guidelines, or policy statements. As of 2001, twelve states had adopted the FSMB's Model Guidelines in full, and nine in part.[42]

It is unclear to what degree the existence of such policies correlates with a board's commitment to educating physicians about pain management and opioid prescribing issues (i.e., to mitigate the chilling effect that has caused physicians to avoid prescribing opioids when they are needed to treat pain). Although the findings reported here must be interpreted cautiously, it appears that boards with state pain policies that address the treatment of chronic, nonmalignant pain are more proactive, in that these boards provide more pain-management-related education to physicians than boards that do not have such policies (see Table 3). However, we do not know whether the content of such educational efforts strives to balance education about overprescribing with that of pain undertreatment concerns. More research is needed to determine what specific messages boards are sending to physicians in these educational efforts, how physicians are interpreting these messages, and how such educational efforts are affecting physicians' opioid prescribing practices.

Respondents' comments indicate that boards are focusing on making their pain policies known to physicians so that physicians are aware of what is required of them to avoid scrutiny by the board. A number of boards emphasized what should be present in the patient's chart to avoid suspicion by the board that the physician is overprescribing (e.g., patient assessment, pain diagnosis, plan of care, evaluation, follow-up, specialist referral). These efforts serve to reassure physicians that they will not be disciplined for overprescribing opioids to patients with chronic pain if they conform to standards of practice and state pain policies. On the other hand, if a physician is accused of overprescribing and lacks proper documentation of his or her practices, he or she is much more likely to be investigated and disciplined.

An encouraging result for pain management advocates is that boards appear to be moving away from volume or

quantity of opioids as a primary basis for investigating a physician for overprescribing opioids. Some respondents referred to volume as a trigger but not conclusive evidence for a decision to investigate. Many respondents indicated that these were very fact-specific cases that had to be evaluated individually; that all facts, including the diagnosis of the patient, the documentation of the prescriptions ordered, and consistency with established guidelines, had to be considered. Despite this positive trend away from using volume as a determinative factor in moving forward to investigate or discipline, a few respondent comments were troublesome in that they implied a continued reliance on volume and, in at least one case, a lack of knowledge regarding issues of dosage and volume. For example, the comment, "It's not based just on dose but quantity.... there comes a point where it's not physically possible to consume so many opioids in such a short period of time," might be accurate if referring to an opioid-naïve patient. However, it is possible that a patient with intractable pain might be administered large doses of opioids with a sharp dose escalation (i.e., large doses in a short period of time) in order to obtain pain relief.[45] Thus, misunderstandings still seem to exist about opioid volume and quantity upper limits (i.e., that the latter exists independently of case-specific facts, which is generally not the case).

In response to the question regarding factors that the board would consider in deciding whether to discipline for overprescribing opioids, most respondents stated that it was a matter of judgment, that it was very fact specific, and often subjective. However, for those that had established pain management policies or guidelines, these appeared key in determining whether to discipline. Significant departures from the policies, in some cases, could be a basis for discipline. Boards varied regarding whether they would require a pattern or more than one instance of overprescribing before disciplining. Poor documentation and recordkeeping were also consistently cited as key factors in disciplining physicians in these cases. A number of boards also mentioned using pain experts to assist them in deciding whether to discipline in cases of overprescribing. A lack of availability of credentialed pain experts may interfere with some boards getting the professional guidance they need to investigate physicians for opioid prescribing practices.

Over half of the respondents (55 percent) thought the number of board disciplinary actions relating to opioid prescribing practices had either stayed the same or decreased over the past 5 years. Respondents who observed a decrease offered reasons that were encouraging for advocates of better pain management. These board representatives thought their board's attitude toward opioid prescribing had changed over the past 5 years and that their pain management guidelines helped them in a number of cases determine that the prescribing practices of the doctor under investigation were

TABLE 3. DIFFERENCES IN EFFORTS TO EDUCATE PHYSICIANS ABOUT PAIN MANAGEMENT BASED ON THE EXISTENCE OF A BOARD POLICY ADDRESSING CHRONIC, NONMALIGNANT PAIN.

PAIN MANAGEMENT EDUCATION/ TRAINING BY BOARD*	BOARDS WITH CHRONIC, NONMALIGNANT PAIN POLICY** ($n = 30$)	BOARDS WITHOUT CHRONIC, NONMALIGNANT PAIN POLICY** ($n = 8$)
Pain management content in newsletter	54% (15 of 28)	17% (1 of 6)
Written pain management materials available/sent to MDs***	40% (12 of 30; 11 sent to MDs)	14% (1 of 7; 1 sent to MDs)
Pain management content in orientation	14% (4 of 28)	0% —
Pain management sessions given by board	47% (14 of 30)	12.5% (1 of 8)

Policies addressing chronic, nonmalignant pain were identified based on the categorization of policies listed on the Pain & Policy Studies Group website. See Pain & Policy Studies Group, University of Wisconsin Comprehensive Cancer Center, Data-base of State Laws, Regulations, and Other Official Government Policies, at <*http://www.medsch.wisc.edu/painpolicy/matrix.htm*> *(last updated November 5, 2002).*

**Respondents were asked: Has your board distributed any educational materials regarding treatment of patients with pain (e.g., copy of guidelines, newsletters, brochures, videos)? Has your board held any educational sessions on treatment of patients with pain? Does the board provide any additional assistance to physicians seeking guidance for the treatment of patients with pain? If respondents answered affirmatively, they were asked to describe the types of materials, sessions, or additional assistance. Information here is based on a content analysis of respondents' comments. Percentages are valid totals. Missing data are the result of respondents who completed a written survey, answered "yes" to any of the questions, but did not provide qualitative elaboration.*

***These are statutes, regulations, guidelines, or policies that address treatment of or opioid prescribing for chronic, nonmalignant pain.*

****These included pain-management-related brochures, copies of pain policies, position statements, and the like that were available upon request and/or distributed to physicians (e.g., by mail or other methods of distribution).*

reasonable, where prior to the adoption of the guidelines they might have disciplined the physician.

The number of estimated complaints boards received for *underprescribing* were significantly fewer than those received for overprescribing (in 2001, an average of 0.46 versus 3.13 complaints, respectively, per 1,000 doctors in the state). A significant majority saw no change in the number of complaints received for underprescribing over the past 5 years. While some respondents thought the problem of pain undertreatment was real and merely underreported, others did not seem to view undertreating pain (particularly chronic, nonmalignant pain) as a significant problem.

While not equivalent to complaints received for overprescribing, it appears that the number of complaints for underprescribing has increased. Martino conducted interviews with medical board executives between November 1997 and January 1998.[46] At that time, only one board (California) of the thirty-six surveyed had received a complaint or report explicitly alleging undertreatment of chronic pain. Several had received complaints from prison inmates alleging that certain medications had been denied as a form of punishment, but they generally were not pursued as pain undertreatment cases.

As regards disciplinary action for undertreating, many boards appear disinclined to discipline simply for violation of standard of care, which is how many respondents depicted cases of underprescribing pain medication. They would be more likely to recommend education to the physicians in such cases. This appeared somewhat at odds with the responses given to questions about disciplining for overprescribing, where respondents said they were more likely to discipline for violation of standard of care, even without a pattern of poor practice. Thus, there is a lack of parity in application of standard of care and patient harm as bases for discipline in cases of undertreatment versus overtreatment. Overprescribing is more often seen as a clear violation of standard of care *and* a clear example of patient harm, while many respondents, or their boards, do not view undertreatment, particularly for chronic pain, in the same way. They appear to apply a higher threshold of harm for undertreating pain.

A number of respondents, however, did provide examples of cases they thought could be construed as gross negligence or egregious behavior regarding pain undertreatment and said that such cases might lead to disciplinary action. Consistent with this response, a significant majority of respondents (79 percent) said that if they were presented with a case where the facts were similar to those of Dr. Bilder (the physician who was disciplined for underprescribing by the Oregon Medical Board), it was either highly likely or probable that they would discipline the physician.

In regard to the potential chilling effect of the board's efforts to oversee opioid prescribing practices, some respondents showed concern that physicians might "go the other way" (i.e., overprescribe opioids if disciplined for undertreating pain, and vice versa). Some boards were working diligently to ease physicians' fears that they would be investigated or disciplined by the board for prescribing opioids to patients. Several thought such fears were completely unfounded or perhaps a convenient excuse to avoid the added work involved in treating chronic pain patients. Others realized that the board's actions had a chilling potential, but thought there was little they could do, that it was the physician's fault for jumping to false conclusions, and that such is the price that is paid for protecting patients. These respondents were aware of the problem of inadequate pain management, but seemed to give more weight to concerns about overprescribing. Respondents spoke of "protecting patients from harm," yet did not view opioid overprescribing and pain undertreatment equally in the degree of public protection they demanded. This type of attitude may contribute to a shortage of physicians who are able and willing to treat patients who have chronic pain. While advocacy for pain management on the part of many state boards may ease physicians' fears about being disciplined for opioid overprescribing, many physicians may decide that their safest (or least burdensome) course is to refer patients with chronic pain to a pain specialist. With the number of patients suffering from chronic pain greatly outnumbering the number of qualified pain specialists, the results do not add up in favor of those with chronic pain.

Conclusion

In sum, we cautiously conclude from our survey results that the attitudes and practices of medical boards toward physicians' prescribing of opioids have changed for the better over the last several years. Respondents' references to the need for "balance" between ensuring appropriate treatment of pain and disciplining physicians who are inappropriately prescribing opioids are illustrative of this movement. The work of a number of individuals and agencies, including the Wisconsin Pain & Policy Studies Group, the American Society of Law, Medicine & Ethics, the Federation of State Medical Boards, through its Model Guidelines, and the recent DEA joint statement, has reinforced this message of the need for balance and may have played a role in moving boards forward on this learning curve. Moreover, boards' abandonment of opioid quantity as a marker of questionable practice, in favor of an individual assessment of whether the physician has appropriately evaluated the patient, prescribed consistent with board guidelines, and appropriately documented his or her prescribing, further indicates progress in board recognition of the need for adequate pain treatment.

At the same time, some attitudes and practices by boards remain problematic — in particular, a continued tolerance of undertreatment. While many boards are becoming more proactive in educating physicians about pain management

issues, the focus is on what physicians who prescribe opioids for pain must do to avoid board scrutiny. There appears to be a discrepancy in the weight given to violation of standard of care, patient harm, and gross negligence for overprescribing as compared to underprescribing. Ironically, boards seem to have a higher threshold for patient harm in cases involving pain undertreatment — particularly for chronic, nonmalignant pain. To this extent, physicians may be getting mixed messages from boards: on the one hand, that effectively managing their patients' pain is the expected standard of care; and on the other hand, that the board is more concerned about opioid overprescribing than underprescribing. Perhaps this is unavoidable given the realities of opioid diversion practices. In terms of lessons one might take away from these findings, reformers may have to accept that management of chronic pain inevitably carries with it a greater chance of entanglement with licensing and law enforcement authorities than management of cancer pain, given the higher risks of diversion.

Acknowledgments

Funding for this study was provided by the Mayday Foundation. The authors would like to acknowledge Aaron Gilson of the Pain & Policy Studies Group at the University of Wisconsin, Sandra Johnson at Saint Louis University School of Law, and Jack Schwartz and Tom Keech at the Maryland State Attorney General's Office, for their helpful input into the design of the survey tool used in this study and/or feedback on earlier versions of this manuscript.

References

1. D.E. Hoffmann, "Undertreating Pain in Women: A Risky Practice," *Journal of Gender-Specific Medicine*, 5 (2002): 10–15, at 12.

2. *Id.* at 12.

3. *Id.*, citing A.M. Martino, "In Search of a New Ethic for Treating Patients with Chronic Pain: What Can Medical Boards Do?," *Journal of Law, Medicine & Ethics*, 26, no. 4 (1998): 332–49, at 332.

4. D.A. Marcus, "Treatment of Nonmalignant Chronic Pain," *American Family Physician*, 61 (2000): 1331–38, 1345–46; R.K. Portenoy, "Opioid Therapy for Chronic Nonmalignant Pain: Clinician's Perspective," *Journal of Law, Medicine & Ethics*, 24, no. 4 (1996): 296–309.

5. A.G. Lipman, "Treatment of Chronic Pain in Osteoarthritis: Do Opioids Have a Clinical Role?," *Current Rheumatology Reports*, 3 (2001): 513–19.; B.H. McCarberg and R.L. Barkin, "Long-Acting Opioids for Chronic Pain: Pharmacotherapeutic Opportunities to Enhance Compliance, Quality of Life, and Analgesia," *American Journal of Therapy*, 8 (2001): 181–86.

6. G.M. Aronoff, "Opioids in Chronic Pain Management: Is There a Significant Risk of Addiction?," *Current Review of Pain*, 4 (2000): 112–21; K.L. Sees and H.W. Clark, "Opioid Use in the Treatment of Chronic Pain: Assessment of Addiction," *Journal of Pain & Symptom Management*, 8 (1993): 257–64.

7. M. Massing, *The Fix* (New York: Simon & Schuster, 1998).

8. S.H. Johnson, "Disciplinary Actions and Pain Relief: Analysis of the Pain Relief Act," *Journal of Law, Medicine & Ethics*, 24, no. 4 (1996): 319–27.

9. C.S. Hill, Jr., "TBS/TCPI Pain Symposium in Conjunction with TexMed 2002," *Texas Pain Bulletin* (July 2002): at description of presentation by Frank Adams, M.D., at the Texas Pain Society and the Texas Cancer Pain Initiative's Symposium, *Opioids, Medicine and the Law*, Dallas, April 19, 2002, *available at* <http://www.texaspain.org/displaycommon.cfm?an=1&subarticlenbr=5>; *Hoover v. Agency for Health Care Administration*, 676 So. 2d 1380 (Fla. Dist. Ct. App. 1996); *In re DiLeo*, 661 So. 2d 162 (La. Ct. App. 1995).

10. C.S. Hill, "The Barriers to Adequate Pain Management with Opioid Analgesics," *Seminars in Oncology*, 20 (1993): 1–5; M.L. Levin et al., "Management of Pain in Terminally Ill Patients: Physician Reports of Knowledge, Attitudes, and Behavior," *Journal of Pain & Symptom Management*, 15 (1998): 27–40.

11. D.Y. Brockopp et al., "Barriers to Change: A Pain Management Project," *International Journal of Nursing Studies*, 35 (1998): 226–32. Research has shown the fears of addiction and overdose or hastened death with opioid use to be highly exaggerated. See M. Bercovitch et al. "High Dose Morphine Use in the Hospice Setting. A Database Survey of Patient Characteristics and Effect on Life Expectancy," *Cancer*, 86 (1999): 871–77; K.J. Boyd and M. Kelly, "Oral Morphine as Symptomatic Treatment of Dyspnoea in Patients with Advanced Cancer," *Palliative Medicine*, 11 (1997): 277–81.

12. See Johnson, *supra* note 8.

13. A. Alpers, "Criminal Act or Palliative Care? Prosecutions Involving the Care of the Dying," *Journal of Law, Medicine & Ethics*, 26, no. 4 (1998): 308–31.

14. J.H. Von Roenn et al., "Physician Attitudes and Practice in Cancer Pain Management. A Survey from the Eastern Cooperative Oncology Group," *Annals of Internal Medicine*, 119 (1993): 121–26.

15. D.C. Turk et al., "Physicians' Attitudes and Practices Regarding the Long-Term Prescribing of Opioids for Non-Cancer Pain," *Pain*, 59 (1994): 201–08.

16. D.E. Weissman et al., "Wisconsin Physicians' Knowledge and Attitudes About Opioid Analgesic Regulations," *Wisconsin Medical Journal*, 90 (1991): 671–75.

17. See Turk et al., *supra* note 15.

18. D.E. Joranson et al., "Pain Management, Controlled Substances, and State Medical Board Policy: A Decade of Change," *Journal of Pain & Symptom Management*, 23 (2002): 138–47, at 140.

19. *Id.*

20. The Mayday Fund was established in 1992 with funds from the estate of the late Shirley Steinman Katzenbach. It is dedicated to the reduction of the physical and psychological effects of pain. See <http://www.painandhealth.org/mayday/mayday-home.html>.

21. FSMB's Model Guidelines were adopted on May 2, 1998. They recommend evaluation of the pain patient by the physician, formulation of a treatment plan, securing informed consent for treatment, performing periodic review of therapy and outcomes, obtaining appropriate consultations or referrals for patients when necessary (e.g., patients with substance abuse history), keeping accurate and complete medical records, and maintaining compliance with controlled substance laws and regulations. See S.H. Johnson, "Introduction: Legal and Regulatory Issues in Pain Management." *Journal of Law, Medicine & Ethics*, 26, no. 4 (1998): 265–66.

22. D.E. Joranson et al., *2001 Annual Review of State Pain Policies: A Question of Balance* (Madison: Pain & Policy Studies Group, University of Wisconsin Comprehensive Cancer Center,

2002), *available at* <www.medsch.wisc.edu/painpolicy/publicat/01annrev/contents.htm>.

23. E. Goodman, "From Oregon, A Call for Compassionate Care," *Boston Globe*, September 9, 1999.

24. "Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act," a Joint Statement from 21 Health Organizations and the Drug Enforcement Administration (October 21, 2001), *available at* <http://www.medsch.wisc.edu/painpolicy/dea01.htm>.

25. See U.S. Drug Enforcement Administration, *OxyContin: Pharmaceutical Diversion*, Drug Intelligence Brief (March 2002), *available at* <http://www.usdoj.gov/dea/pubs/intel/02017/02017.html>.

26. B. Meier, "OxyContin Prescribers Face Charges in Fatal Overdoses," *New York Times*, January 19 2002; B. Meier, "A Small Town Clinic Looms Large as a Top Source of Disputed Painkillers," *New York Times*, February 10, 2001.

27. Individuals who reviewed the draft survey include: Aaron Gilson from the Pain & Policy Studies Group at the University of Wisconsin, Sandra Johnson from Saint Louis University School of Law, Jack Schwartz and Tom Keech from the Maryland State Attorney General's Office, Kathryn Tucker from Compassion in Dying, and Irwin Weiner, a retired physician board member of the Maryland Board of Physician Quality Assurance.

28. The survey was designed to be administered during a phone interview, but a minority of respondents opted to complete the survey in written form.

29. See Pain & Policy Studies Group, University of Wisconsin Comprehensive Cancer Center, *Data-base of State Laws, Regulations, and Other Official Government Policies*, *at* <http://www.medsch.wisc.edu/painpolicy/matrix.htm> (last updated November 5, 2002).

30. See Pain & Policy Studies Group, University of Wisconsin Comprehensive Cancer Center, *Prescription Monitoring Programs*, *at* <http://www.medsch.wisc.edu/painpolicy/domestic/diversion.htm> (last visited February 12, 2003).

31. In addition to formal written complaints, twenty-two of the thirty-eight respondents also accepted complaints by phone, e-mail, or anonymously, although anonymous complaints were investigated only in rare circumstances (i.e., regarding serious complaints when sufficient information was provided to investigate further). Some states first considered allegations that were transformed into complaints after a formal process in which preliminary evidence was collected.

32. This could include complaints against physicians for prescribing opioids for pain patients they were treating, prescribing for themselves, or trading opioids for money or sex.

33. This is consistent with the findings of Weiner and Pound in their "Project on Legal Constraints on Access to Effective Pain Relief," in which they interviewed medical board members (cited in Johnson, *supra* note 8, at 321), and found that the boards were "not able to separate actions against physicians treating patients for pain from the more general disciplinary category of abuse of prescription drugs."

34. The actual range of values was 0 to 250. To correct for the outlier values of 100 and 250, these values were "windsorized" to the next highest values of 57 and 58, respectively. Those numbers were then divided by the number of physicians per state (see data at <http://www.education-world.com/a_lesson/TM/WS_census_states.shtml>) and multiplied by 1,000.

35. The task of investigating and disciplining physicians was implemented by different individuals, departments, or agencies, depending on the structure of the board and whether it was part of an "umbrella" agency. When referring to boards' investigating or disciplining physicians, we are referring to whatever mechanism the individual board implements to investigate or discipline physicians in that particular state.

36. See Pain & Policy Studies Group, *supra* note 29.

37. The lowest dose of OxyContin is 10 mg. An opioid-naïve patient with chronic pain is typically started on 10 mg of OxyContin twice a day, and the dose is increased until the patient's pain is controlled (unless the pain is refractory to opioid therapy or other circumstances exist). Suggested dosing for OxyContin is twice a day or every 12 hours, not four times a day. Patients with cancer pain are more likely than patients with chronic nonmalignant pain to take larger daily doses, but there is usually no way of knowing by daily mg dosing alone whether a physician has overprescribed OxyContin for an individual patient.

38. The respondent conveyed that referral to a pain management specialist would be expected for primary care physicians treating patients with complex chronic pain.

39. Eighteen respondents thought their boards had not received any such complaints — their pain undertreatment complaint estimate was entered as zero. Of the nineteen who thought their boards had received such complaints, fifteen were able to give a 2001 estimate. If a range was given, the median of the range was entered. The actual range of values was 0 to 25. To correct for the outlier value of 25, that value was "windsorized" to the next highest value of 13. Raw values were then divided by the number of physicians per state (see data at <http://www.education-world.com/a_lesson/TM/WS_census_states.shtml>) and multiplied by 1,000.

40. We specifically asked about prisoners as a source of complaints, as they tend to file complaints with state medical boards regarding poor medical care in general. One respondent said he "tended to investigate most prisoner complaints because they're in a duress situation; they might not get the best care," while another commented, "Some department of corrections issues, like prisoners' being undertreated, we don't investigate. Even if it's true, are we going to do anything about it?"

41. Estimates for four of the five respondents whose boards had not used a pain management expert were entered as zero (one reported no cases of pain undertreatment complaints and did not know the number of opioid overprescribing complaints. We did not assume that this board had complaints about opioid prescribing to investigate, so we considered data for that board as missing). Of the twenty-three respondents whose boards had used a pain management expert and who gave an estimate of the percentage of investigations in which such an expert was used, if a range was given, the median of the range was entered.

42. Joranson et al., *supra* note 22.

43. The following scenarios may also indicate inappropriate quantities of opioids being prescribed: (1) the doctor is prescribing relatively low dose tablets but in great volume and does not know to shift the patient to a higher dose, a longer acting version, or a different drug, when the current drug is no longer effective; (2) the doctor may be prescribing in the hundreds of tabs a day. However, focusing on quantity alone is generally insufficient to determine that a physician is overprescribing.

44. See Martino, *supra* note 3.

STATE PROHIBITIONS AGAINST SELF AND FAMILY PRESCRIBING

The Uniform Controlled Substances Act provides:

> SECTION 308. **PRESCRIPTIONS**. [...] (i) An individual practitioner may not dispense a substance included in Schedule II, III, or IV for that individual practitioner's personal use except in a medical emergency.
>
> *Comment:* [...] "Dispense" is defined in Section 101(5) to include prescribe, administer, package, label, and compound. [...]
>
> The Uniform Controlled Substances Act, completed by the Uniform Law Commissioners in 1970 and amended in 1973, was subsequently adopted in 46 states. The Revised Uniform Controlled Substances Act was completed by the Uniform Law Commissioners in 1990, and amended in 1994. The 1990 RUCSA has been adopted by Colorado (which did not include the self-prescribing paragraph), Nevada, and Wisconsin.

Arizona has the following statute:

> ARS § 32-1401, "Unprofessional conduct" includes the following, whether occurring in this state or elsewhere: [...] (g) Using controlled substances except if prescribed by another physician for use during a prescribed course of treatment.
> (h) Prescribing or dispensing controlled substances to members of the physician's immediate family.

California has the following statute:

> Cal. Bus. & Prof. Code §2239(a) The use or prescribing for or administering to himself or herself, of any controlled substance; or the use of any of the dangerous drugs specified in Section 4022, or of alcoholic beverages, to the extent, or in such a manner as to be dangerous or injurious to the licensee, or to any other person or to the public, or to the extent that such use impairs the ability of the licensee to practice medicine safely or more than one misdemeanor or any felony involving the use, consumption, or self-administration of any of the substances referred to in this section, or any combination thereof, constitutes unprofessional conduct. The record of the conviction is conclusive evidence of such unprofessional conduct.

Florida has the following statute:

> Fla. Stats. §458.331 **Grounds for disciplinary action; action by the board and department.**
> (1) The following acts constitute grounds for denial of a license or disciplinary action, as specified in s. 456.072(2): [...]
> (r) Prescribing, dispensing, or administering any medicinal drug appearing on any schedule set forth in chapter 893 by the physician to himself or herself, except one

prescribed, dispensed, or administered to the physician by another practitioner authorized to prescribe, dispense, or administer medicinal drugs.

Hawaii has adopted the language of the RUCSA, prohibiting self-prescribing.

Idaho has the following administrative rules:

IDAPA §27.01.01.454. **Prescribing For Self Prohibited:** No person shall prescribe, administer or furnish a controlled substance for himself.
IDAPA §22.01.01.101 **Additional Grounds For Suspension, Revocation Or Disciplinary Sanctions.** [...] 03. **Standard of Care.** [...]
d. Prescribing, selling, administering, distributing or giving any drug legally classified as a controlled substance or recognized as an addictive or dangerous drug to himself or herself or to a spouse, child or stepchild.

Massachusetts has the following administrative rule:

243 CMR §2.07: **General Provisions Governing The Practice Of Medicine** [...] (19) Self-Prescribing and Prescribing for Family Members. A licensee is prohibited from prescribing controlled substances in Schedules II, III, and IV for his own use. Except in an emergency, a licensee is prohibited from prescribing Schedule II controlled substances to a member of his immediate family, including a spouse (or equivalent), parent, child, sibling, parent-in-law, son/daughter-in-law, brother/sister-in-law, step-parent, step-child, step-sibling, or other relative permanently residing in the same residence as the licensee.

Nevada has adopted the RUCSA's prohibition on self-prescribing.

South Dakota has the following administrative rules:

ARSD §44:58:08:05. **Manner of issuance of prescriptions.** No practitioner may issue a prescription for a controlled substance for the practitioner's use.
ARSD §44:58:08:11.01. **Direct administering or dispensing of controlled substances.** An individual practitioner, in the course of professional practice only, may directly administer or dispense a controlled substance without a prescription to other persons. An individual practitioner or institutional practitioner may not order a controlled substance for direct administration or dispense a controlled substance, including any controlled substance sample, for the practitioner's use.

Virginia Board of Medicine Guidance Document 85-8 (Excerpt from Board Briefs #60, Summer 2000) states:

Self-Prescribing
1. A physician cannot have a bona fide doctor/patient relationship with himself or herself.
2. Only in an emergency should a physician prescribe for himself or herself schedule VI drugs.
3. Prescribing of schedule II, III, IV, or V drugs to himself or herself is prohibited.

Immediate Family
1. Treatment of immediate family members should be reserved only for minor illnesses or emergency situations.
2. Appropriate consultation should be obtained for the management of major or extended periods of illness.
3. No schedule II, III or IV controlled substances should be dispensed or prescribed except in emergency situations.
4. Records should be maintained of all written prescriptions or administration of any drugs.

Wisconsin has adopted the UCSA's prohibition on self-prescribing, without the "emergency" exception.

Washington has adopted the USCA's prohibition on self-prescribing.

Wyoming has the following administrative rule:

> 33-26-402. **Grounds for suspension; revocation; restriction; imposition of conditions; refusal to renew or other disciplinary action.** (a) The board may refuse to renew, and may revoke, suspend or restrict a license or take other disciplinary action, including the imposition of conditions or restrictions upon a license on one (1) or more of the following grounds: […]
> (xii) Repeatedly prescribing, selling, supplying or administering any drug legally classified as a narcotic, addicting or scheduled drug to a parent, spouse or child of the applicant or licensee, or to himself;

Irrespective of state criminal law, self-prescribing, and prescribing for one's family, of controlled substances is unethical in non-emergency cases, see AMA Ethics Opinion:

> **E-8.19 Self-Treatment or Treatment of Immediate Family Members.**
>
> Physicians generally should not treat themselves or members of their immediate families. Professional objectivity may be compromised when an immediate family member or the physician is the patient; the physician's personal feelings may unduly influence his or her professional medical judgment, thereby interfering with the care being delivered. Physicians may fail to probe sensitive areas when taking the medical history or may fail to perform intimate parts of the physical examination. Similarly, patients may feel uncomfortable disclosing sensitive information or undergoing an intimate examination when the physician is an immediate family member. This discomfort is particularly the case when the patient is a minor child, and sensitive or intimate care should especially be avoided for such patients. When treating themselves or immediate family members, physicians may be inclined to treat problems that are beyond their expertise or training. If tensions develop in a physician's professional relationship with a family member, perhaps as a result of a negative medical outcome, such difficulties may be carried over into the family member's personal relationship with the physician.

Concerns regarding patient autonomy and informed consent are also relevant when physicians attempt to treat members of their immediate family. Family members may be reluctant to state their preference for another physician or decline a recommendation for fear of offending the physician. In particular, minor children will generally not feel free to refuse care from their parents. Likewise, physicians may feel obligated to provide care to immediate family members even if they feel uncomfortable providing care.

It would not always be inappropriate to undertake self-treatment or treatment of immediate family members. In emergency settings or isolated settings where there is no other qualified physician available, physicians should not hesitate to treat themselves or family members until another physician becomes available. In addition, while physicians should not serve as a primary or regular care provider for immediate family members, there are situations in which routine care is acceptable for short-term, minor problems.

Except in emergencies, it is not appropriate for physicians to write prescriptions for controlled substances for themselves or immediate family members. (I, II, IV) Issued June 1993.

i:\pain.rx.selfprescribing.states.doc 11/5/2004 9:45 AM

Advocacy & Policy

Definitions Related to the Use of Opioids for the Treatment of Pain:

A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine

American Pain Society

Back to Full Page

Inconsistent use of the terms addiction, dependence and tolerance, often results in misunderstandings between regulators, health care providers, patients and the general public regarding the use of medications for the treatment of pain. Because of these misunderstandings, pain is often under-treated and individuals may be stigmatized because of their use of opioids for medical purposes.

The Liaison Committee on Pain and Addiction (CPA) has developed definitions related to the use of medications for the treatment of pain that are consistent with current understanding of relevant neurobiology, pharmacology and appropriate clinical practice. The ultimate goal of this project is to achieve acceptance and use of uniform definitions by clinicians, regulators and the public, both nationally and internationally, in order to promote appropriate treatment of pain throughout the world. The definitions have been approved by each of the three collaborating organizations.

The Liaison Committee on Pain and Addiction is a collaborative effort of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. The committee members included Seddon Savage, MD, Chair; Edward C. Covington, MD; Howard A. Heit, MD; John Hunt, MD; David Joranson, MSSW; and Sidney H. Schnoll, MD PhD.

Background

Clear terminology is necessary for effective communication regarding medical issues. Scientists, clinicians, regulators, and the lay public use disparate definitions of terms related to addiction. These disparities contribute to a misunderstanding of the nature of addiction and the risk of addiction, especially in situations in which opioids are used, or are being considered for use, to manage pain. Confusion regarding the treatment of pain results in unnecessary suffering, economic burdens to society, and inappropriate adverse actions against patients and professionals.

Many medications, including opioids, play important roles in the treatment of pain. Opioids, however, often have their utilization limited by concerns regarding misuse, addiction, and possible diversion for non-medical uses.

Many medications used in medical practice produce dependence, and some may lead to addiction in vulnerable individuals. The latter medications appear to stimulate brain reward mechanisms; these include opioids, sedatives, stimulants, anxiolytics, some muscle relaxants, and cannabinoids.

Physical dependence, tolerance, and addiction are discrete and different phenomena that are often confused. Since their clinical implications and management differ markedly, it is important that uniform definitions, based on current scientific and clinical understanding, be established in order to promote better care of patients with pain and other conditions where the use of dependence-producing drugs is appropriate, and to encourage appropriate regulatory policies and

enforcement strategies.

Recommendations

The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine recognize the following definitions and recommend their use.

Addiction
Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Physical Dependence
Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Tolerance
Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Discussion

Most specialists in pain medicine and addiction medicine agree that patients treated with prolonged opioid therapy usually do develop physical dependence and sometimes develop tolerance, but do not usually develop addictive disorders. However, the actual risk is not known and probably varies with genetic predisposition, among other factors. Addiction, unlike tolerance and physical dependence, is not a predictable drug effect, but represents an idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals. Most exposures to drugs that can stimulate the brain's reward center do not produce addiction. Addiction is a primary chronic disease and exposure to drugs is only one of the etiologic factors in its development.

Addiction in the course of opioid therapy of pain can best be assessed after the pain has been brought under adequate control, though this is not always possible. Addiction is recognized by the observation of one or more of its characteristic features: impaired control, craving and compulsive use, and continued use despite negative physical, mental, and/or social consequences. An individual's behaviors that may suggest addiction sometimes are simply a reflection of unrelieved pain or other problems unrelated to addiction. Therefore, good clinical judgment must be used in determining whether the pattern of behaviors signals the presence of addiction or reflects a different issue.

Behaviors suggestive of addiction may include: inability to take medications according to an agreed upon schedule, taking multiple doses together, frequent reports of lost or stolen prescriptions, doctor shopping, isolation from family and friends, and/or use of non-prescribed psychoactive drugs in addition to prescribed medications. Other behaviors which may raise concern are the use of analgesic medications for other than analgesic effects, such as sedation, an increase in energy, a decrease in anxiety, or intoxication; non-compliance with recommended non-opioid treatments or evaluations; insistence on rapid-onset formulations/routes of administration; or reports of no relief whatsoever by any non-opioid treatments.

Adverse consequences of addictive use of medications may include persistent sedation or intoxication due to overuse; increasing functional impairment and other medical complications; psychological manifestations such as irritability, apathy, anxiety, or depression; or adverse legal, economic or social consequences. Common and expected side effects of the medications, such as constipation or sedation due to use of prescribed doses, are not viewed as adverse consequences in this context. It should be emphasized that no single event is diagnostic of addictive disorder. Rather, the diagnosis is made in response to a pattern of behavior that usually becomes obvious over time.

Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.

Physical dependence on and tolerance to prescribed drugs do not constitute sufficient evidence of psychoactive substance use disorder or addiction. They are normal responses that often occur with the persistent use of certain medications. Physical dependence may develop with chronic use of many classes of medications. These include beta blockers, alpha-2 adrenergic agents, corticosteroids, antidepressants, and other medications that are not associated with addictive disorders. When drugs that induce physical dependence are no longer needed, they should be carefully tapered while monitoring clinical symptoms to avoid withdrawal phenomena and such effects as rebound hyperalgesia. Such tapering, or withdrawal, of medication should not be termed detoxification. At times, anxiety and sweating can be seen in patients who are dependent on sedative drugs, such as alcohol or benzodiazepines, and who continue taking these drugs. This is usually an indication of development of tolerance, though the symptoms may be due to a return of the symptoms of an underlying anxiety disorder, due to the development of a new anxiety disorder related to drug use, or due to true withdrawal symptoms.

A patient who is physically dependent on opioids may sometimes continue to use these despite resolution of pain only to avoid withdrawal. Such use does not necessarily reflect addiction.

Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. For example, in the case of opioids, tolerance usually develops more slowly to analgesia than to respiratory depression, and tolerance to the constipating effects may not occur at all. Tolerance to the analgesic effects of opioids is variable in occurrence but is never absolute; thus, no upper limit to dosage of pure opioid agonists can be established.

Universal agreement on definitions of addiction, physical dependence, and tolerance is critical to the optimization of pain treatment and the management of addictive disorders. While the definitions offered here do not constitute formal diagnostic criteria, it is hoped that they may serve as a basis for the future development of more specific, universally accepted diagnostic guidelines. The definitions and concepts that are offered here have been developed through a consensus process of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine.

This document was prepared by the following committee members: Seddon Savage, MD (Chair) - APS; Edward C. Covington, MD - AAPM; Howard A. Heit, MD - ASAM; John Hunt, MD - AAPM; David Joranson, MSSW - APS; and Sidney H. Schnoll, MD, PhD - ASAM.

Approved by the AAPM Board of Directors on February 13, 2001
Approved by the APS Board of Directors on February 14, 2001
Approved by the ASAM Board of Directors on February 21, 2001

American Academy of Pain Medicine
4700 W. Lake Avenue
Glenview, IL 60025-1485
847/375-4731
Fax 877/734-8751
E-mail aapm@amctec.com
http://www.painmed.org/

American Pain Society
4700 W. Lake Avenue
Glenview, IL 60025-1485
847/375-4715
Fax 877/734-8758
E-mail info@ampainsoc.org
http://www.ampainsoc.org/

American Society of Addiction Medicine
4601 North Park Avenue
Arcade 101
Chevy Chase, MD 20815
301/656-3920
Fax 301/656-3815
E-mail email@asam.org
http://www.asam.org/

Public Policy Statement on the Rights and Responsibilities of Healthcare Professionals in the use of Opioids for the Treatment of Pain

A consensus document from the **American Academy of Pain Medicine**, *the* **American Pain Society**, *and the* **American Society of Addiction Medicine.**

BACKGROUND

Healthcare professional (HCP) concerns regarding the potential for harm to patients, as well as possible legal, regulatory, licensing or other third party sanctions related to the prescription of opioids, contribute significantly to the mistreatment of pain. HCPs are obligated to act in the best interest of their patients. This action may include the addition of opioid medication to the treatment plan of patients whose symptoms include pain. Though many types of pain are best addressed by non-opioid interventions, opioids are often indicated as a component of effective pain treatment. It is sometimes a difficult medical judgment as to whether opioid therapy is indicated in patients complaining of pain because objective signs are not always present.

A decision whether to prescribe opioids may be particularly difficult in patients with concurrent addictive disorders, or with risk factors for addiction, such as a personal or family history of addictive disorder. For such persons, exposure to potentially rewarding substances may reinforce drug taking behavior and therefore present special risks. It is, nonetheless, a medical judgment that must be made by a HCP in the context of the provider-patient relationship based on knowledge of the patient, awareness of the patient's medical and psychiatric conditions and on observation of the patient's response to treatment. The selection of a particular opioid, or combination of opioids, and the determination of opioid dose and therapeutic schedule similarly must be based on full clinical understanding of a particular situation and cannot be judged appropriate or inappropriate independent of such knowledge. All schedule II-V opioids, including methadone, may be appropriate choices for pain control in different circumstances; it is critical that clinicians understand the special pharmacologic characteristics of each medication in order to prescribe them safely and effectively for pain.

Despite appropriate medical practice, healthcare providers who prescribe opioids for pain may occasionally be misled by patients who wish to obtain medications for purposes other than pain treatment, such as diversion for profit, recreational use or perpetuation of an addicted state. Physicians who are willing to provide compassionate, ongoing medical care to challenging and psychosocially stressed patients, where that treatment includes the prescription of opioids, assume an additional obligation to understand the risks and management of addictive disease because they risk complications of care more often than physicians unwilling to treat this population.

Addiction to opioids may occur despite appropriate opioid therapy for pain in some susceptible individuals. Persistent failure to recognize and provide appropriate medical treatment for the disease of addiction is poor medical practice and may become grounds for practice concern. Similarly, persistent failure to use opioids effectively when they are indicated as part of the treatment of pain, including in persons with active or recovering addiction, is poor medical practice and may also become grounds for practice concern. It is important to distinguish, however, between HCPs who are knowingly complicit in diversion or other illegal prescribing activities and physicians who may inappropriately prescribe opioids due to misunderstandings regarding addiction or pain. HCPs traditionally have received little or no education on addiction or clinical pain treatment in the course of training. This omission is likely a basis for inadequate detection and management of addiction and inadequate assessment and treatment of pain.

RECOMMENDATIONS

1. Healthcare professionals (HCPs) who prescribe opioids for the treatment of pain should use clear and reasonable medical judgment to establish that a pain state exists and to determine whether opioids are an indicated component of treatment. Opioids should be prescribed in a lawful and clinically sound manner. Patients should be followed at reasonable intervals for ongoing medical management, to confirm as nearly as is reasonable that the medications are used as prescribed, that the goals of treatment are met and to revise therapy as indicated. Such initial decision-making and ongoing management should be appropriately documented.

2. HCPs who are practicing medicine in good faith and who use reasonable medical judgment regarding the prescription of opioids for the treatment of pain should not be held responsible for the willful and deceptive behavior of patients who successfully obtain opioids for non-medical purposes. It is an appropriate role of the DEA, pharmacy boards and other regulatory agencies to inform physicians of the behavior of such patients when it is detected.

3. Interventions to correct the clinical care practices of HCPs who consistently fail to recognize addictive disorders, medication misuse, or medication diversion in their patients are appropriate. Interventions may include education and/or licensing or legal sanction as indicated after careful and appropriate review of records and other available information.

4. Interventions to correct the clinical care practices of HCPs who consistently fail to appropriately evaluate and treat pain in their patients are appropriate. Interventions may include education and/or licensing or legal sanction as indicated after careful and appropriate review of records and other available information.

5. For the purpose of performing regulatory, legal, quality assurance and other clinical case reviews, it should be recognized that judgment regarding a) the medical appropriateness of the prescription of opioids for pain in a specific context, b) the selection of a particular opioid drug or drugs, and c) the determination of indicated opioid dosage and interval of medication administration, can only be made properly with full and detailed understanding of a particular clinical case.

6. Regulatory, legal, quality assurance and other reviews of clinical cases involving the use of opioids for the treatment of pain should be performed, when they are indicated, by reviewers with a requisite level of understanding of pain medicine and addiction medicine.

7. Appropriate education in addiction medicine and pain medicine should be provided as part of the core curriculum at all medical and other provider training schools.

8. Legal and/or licensing actions against HCPs who are proven to be knowingly complicit in the diversion of scheduled drugs or other illegal prescribing activities are appropriate.

This document was prepared by the following committee members: Seddon Savage, MD (Chair) - APS; Edward C. Covington, MD - AAPM; Aaron M. Gilson, PhD – APS; Douglas Gourlay – ASAM; Howard A. Heit, MD - ASAM; and John B. Hunt, MD – AAPM.

Adopted by AAPM Board of Directors, March 2004

Adopted by APS Board of Directors, March 2004

Adopted by ASAM Public Policy Committee, January 2004

4700 W. Lake Avenue
Glenview, IL 60025-1485
847/375-4731
Fax 877/734-8751
E-mail aapm@amctec.com
www.painmed.org

American Pain Society
4700 W. Lake Avenue
Glenview, IL 60025-1485
847/375-4715
Fax 877/734-8758
E-mail info@ampainsoc.org
www.ampainsoc.org

4601 North Park Avenue
Arcade Suite 101
Chevy Chase, MD 20815
301/656-3920
Fax 301/656-3815
E-mail email@asam.org
www.asam.org

THERAPY IN PRACTICE

Drugs 2003; 63 (1): 17-32
0012-6667/03/0001-0017/$33.00/0

Responsible Prescribing of Opioids for the Management of Chronic Pain

Bruce Nicholson

Lehigh Valley Hospital Pain Center, Allentown, Pennsylvania, USA

Contents

Abstract

The management of patients with chronic pain is a common clinical challenge. Indeed, chronic pain is often inadequately controlled in patients with cancer and in those with non-cancer chronic pain. Because of the complex nature of chronic pain, successful long-term treatment is more difficult than for acute pain. Most often acute pain is nociceptive, whereas chronic pain can be nociceptive (i.e., in

response to noxious stimuli), neuropathic (i.e., initiated by a primary lesion or dysfunction in the nervous system) or mixed in origin.

Opioids are the current standard of care for the treatment of moderate or severe nociceptive pain. Opioids mediate their actions by binding and activating receptors both in the peripheral nervous system and those that are found in inhibitory pain circuits that descend from the midbrain to the spinal cord dorsal horn. Opioid agonists exert a number of physiological responses including analgesia, which increases with increasing doses.

The use of opioids to manage pain in patients with cancer is well accepted. The WHO step-wise algorithm for analgesic therapy based on pain severity reserves the use of opioid therapy for moderate and severe pain. The WHO algorithm has proven to be highly effective for the management of cancer pain. However, the use of opioids to treat patients with chronic non-cancer pain is controversial because of concerns about efficacy and safety, and the possibility of addiction or abuse. The results of clinical surveys and retrospective case series involving patients with non-cancer chronic pain have been inconsistent in regard to resolving these controversial issues.

The oral route of drug administration is most appropriate for patients receiving opioids; although rectal, transdermal and parenteral routes of administration are used in specific situations. For continuous chronic pain, opioids should be administered around-the-clock and several long-acting formulations are available that require administration only once or twice daily. Opioid doses should be titrated according to agent-specific schedules to maximise pain relief and maintain tolerability. Adverse effects include constipation, nausea and vomiting, sedation, cognitive impairment and respiratory depression. Tolerance to the analgesic and adverse effects as well as physical dependence, which causes withdrawal symptoms upon discontinuance, may occur with opioid use. Estimates of addiction rates among patients with chronic non-cancer pain range from 3.2 to 18.9%.

Successful pain treatment and symptom management is an attainable goal for the majority of patients with chronic pain. Further controlled clinical trials are needed to define the role of opioid therapy in chronic non-cancer pain, and to establish criteria for patient selection and specific treatment algorithms.

1. Chronic Pain and the Use of Opioids

Over the past 10–20 years, several studies were published documenting inadequate pain control in patients with postoperative, cancer and non-malignant chronic pain.[1-4] This information spurred professional societies and governmental and regulatory agencies to develop standards and guidelines for the management of acute and cancer pain.[5] These organisations, which included the WHO, the International Association for the Study of Pain (IASP), the US Agency for Health Care Policy and Research (AHCPR), and the Joint Commission for Accreditation of Healthcare Organisations (JCAHO), continue to work toward the humane goals of relieving unnecessary pain and improving patient quality of life. While successful in changing many of the perceptions and practices of healthcare professionals who treat pain, barriers, limitations and controversies remain, particularly in the treatment of chronic pain. This article reviews the role of commonly used opioids for the treatment of chronic pain, with a focus on selecting treatments based on the individual patient's need for pain control.

2. Pain Definitions

The IASP defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'.[6] Pain is generally categorised as acute or chronic. Acute pain serves the necessary function of alerting the body to harmful or potentially harmful stimuli. It occurs because of trauma, a medical or surgical procedure, or a disease flare concomitant to a chronic medical condition. Acute pain typically is of short duration and its treatment is relatively straightforward.[7] In contrast, chronic pain is far more complex and difficult to treat. It persists longer than 3–6 months – beyond the time that healing normally occurs. While it is frequently associated with disease processes such as cancer, AIDS, rheumatoid arthritis and osteoarthritis, it also occurs in disorders that do not have a specific diagnosis, such as low back pain and failed back surgery.[7] Chronic pain syndromes unfortunately are quite common. From estimates of the prevalence of individual conditions, Bonica concluded that one in three Americans experiences chronic pain.[8] Table I provides characteristics of chronic pain.

Chronic pain can be nociceptive, neuropathic or mixed in origin. Nociceptive pain initiates when primary afferent nociceptors in the peripheral nervous system – Aδ fibres and C fibres – are activated by noxious thermal, mechanical or chemical stimuli secondary to tissue injury. After peripheral stimulation, information is transmitted to second-order projection neurones in the dorsal horn of the spinal cord, where pain signals are interpreted and modulated. Second-order projection neurones then transmit pain signals through several ascending tracts that terminate throughout the brain stem, thalamus and cortex. The transmission of impulses in ascending pathways is modified by endogenous opiates, as well as non-opiate inhibitory influences from descending pathways that moderate pain.[9] Pain perception reflects a complex interplay between stimulation and inhibition.

Table I. Characteristics of chronic pain

Pain lasting beyond the time that normal healing occurs (>3–6 months)
Associated with specific and non-specific medical conditions:
cancer
AIDS
rheumatoid arthritis
osteoarthritis
low back pain
spinal stenosis
failed back surgery
Estimated to occur in one of every three Americans
May be nociceptive and/or neuropathic in origin

Neuropathic pain is caused or initiated when tissue injury leads to a primary lesion or dysfunction in the nervous system itself.[6] Accumulating evidence suggests that a key pathogenic event in neuropathic pain occurs in the central nervous system (CNS). A continuing barrage of spontaneous pain signals from damaged C fibre nociceptors causes spinal cord neurones in the dorsal horn to become hyperexcitable, a phenomenon known as central sensitisation. Central sensitisation manifests in symptoms such as hyperalgesia, a heightened response to pain, and secondary hyperalgesia, pain sensitivity beyond the primary site of tissue injury. Over time, allodynia, the sensation of pain from a normally non-painful stimulus, also can develop as a result of abnormal central processing of input from Aβ fibres.[10,11] While central sensitisation is recognised to be a critical element, the development of neuropathic pain is a complex process involving numerous putative mechanisms. Chronic pain is the end result of an interplay of pathogenic mechanisms that may be nociceptive, neuropathic or mixed in origin.

Studies in experimental animal models suggest that chronic exposure to opioids can have the paradoxical effect of inducing a state of hyperexcitability in the CNS. Rohde and colleagues have shown that the tolerance that occurs with long-term exposure to morphine has features in common with central sensitisation.[12] The clinical relevance of these findings remains to be fully explored. Some have suggested that this phenomenon in part explains the limited utility of opioids

in non-nociceptive pain that has been demonstrated in some, but not all, clinical studies.[13,14]

3. Opioid Actions

Opioids are the current standard of care for the treatment of moderate to severe pain. In fact, they have been the mainstay of pain treatment for thousands of years.[15] In ancient times, opium, which is derived from the juice of the opium poppy, *Papaver somniferum*, was used to fight cough and diarrhoea, and to relieve pain through its euphoria-inducing properties.[16] Opium contains more than 20 active alkaloid compounds, of which morphine is the most potent and was the first to be isolated, in 1806.[15] The purification of other compounds from opium soon followed and widespread use of purified agents began in the mid-nineteenth century. Currently available opioid drugs include products directly derived from opium, such as morphine, codeine and thebaine, and their many semi-synthetic derivatives.[15]

Opioids mediate their actions by binding and activating receptors that comprise part of an endogenous descending pathway that normally operates to modulate pain. Endogenous opioid peptides (met-enkephalin, leu-enkephalin, β-endorphin, dynorphin A, dynorphin B, α-neoendorphin) and opioid receptors are found throughout inhibitory pain circuits, which descend from the midbrain via the rostral ventromedial medulla to the spinal cord dorsal horn.[15] Opioid receptors and endogenous opioid peptides also have been identified in the peripheral nervous system. During inflammation, endogenous opioids secreted by immune and inflammatory cells have been shown to activate opioid receptors on sensory nerve terminals to inhibit nociception.[17]

Opioid receptors consist of three subtypes: μ (mu), δ (delta) and κ (kappa). Most of the clinically useful opioid drugs, for which morphine serves as the prototype, are relatively selective for μ receptors. These drugs are full agonists. Their interactions with opioid receptors stimulate physiological responses. In addition to analgesia, stimulation of μ receptors affects mood and rewarding behaviour, and alters respiratory, cardiovascular, gastrointestinal and neuroendocrine functions.[15] Full agonists have no ceiling to their analgesia. Analgesia increases as the dose is raised until adequate pain control is achieved or dose-limiting adverse effects occur.[18] In practice, this requires dose escalation to identify the balance between maximum analgesic efficacy and tolerability of adverse effects.[18]

4. Considerations in Chronic Pain Management

It is well recognised that patient responses to pain as well as to different opioid agents can be highly variable.[19] Dose escalation in one patient may result in successful pain relief, whereas the same agent in another patient may cause intolerable adverse effects without adequate pain control. While the mechanisms that underlie these differences are not well understood, it is obvious that clinicians must be knowledgeable in the use of commonly available agents in order to effectively individualise treatment.[15] In addition, they must know general principles of opioid treatment: whom to treat; how to match analgesic therapy to pain severity; available routes of administration; appropriate dose administration regimens; dosage levels for treatment initiation and titration; common adverse events; and effects of opioid therapy such as tolerance to most adverse effects and physical dependence. An overview of these issues and of commonly available agents is provided in the following subsections.

4.1 Patient Selection

Opioid therapy is the cornerstone of pain management in patients with cancer or those who are terminally ill. The role of opioids in relieving moderate to severe pain in these patient populations is universally accepted and supported. In contrast, the use of opioids to relieve pain in patients with chronic non-cancer pain remains quite controversial. This controversy is based on concerns that opioids may be ineffective, unsafe, and lead to addiction or abuse.[20] The substantial clinical experience in patients with cancer has been encouraging. Not

only have opioids proved to be effective and 'safe', but also problems stemming from addiction or abuse have been minimal.[20,21] However, there are further concerns that opioid therapy in patients with chronic non-cancer pain would shift the patient's sense of control toward an external agent for relief of pain, engendering a sense of dependency on the medical system, and neglecting other treatment goals such as increased function and return to normal activities.[22]

There are few good data on the efficacy of opioids in patients with chronic non-cancer pain. Clinical surveys and case series have provided much of the published information. Overall, large clinical surveys generally reported favourable outcomes in selected patients.[20,21] On the other hand, retrospective case series, most of which originated from pain management programmes, reported few treatment benefits.[20,21] Several randomised clinical trials have sought to determine whether opioids are effective in patients with neuropathic pain (extensively reviewed by Dellemijn[23]). Results were variable: some studies found clear dose-response analgesic effects in patients with neuropathic pain, while others suggested that opioids were ineffective.[14,21,23] There have also been a number of randomised trials that have specifically evaluated the long-term efficacy of opioids in patients with chronic non-cancer pain (reviewed by Dickinson et al.[21]).[24-28] These studies have uniformly shown that opioids are effective in relieving pain, but effects of opioid treatment on disability, emotional distress, quality of life, and psychological or functional improvements have been variable.[21] For example, one study in patients with back pain found that patients reported significantly less pain and improved mood, but few differences were found in activity or hours asleep.[26]

Despite these mixed findings, there are subgroups of patients with chronic non-cancer pain who benefit from regular administration of opioid drugs.[27] Overall, studies have suggested that patients with nociceptive pain are the most responsive to opioids and derive the most benefit from long-term treatment. Moreover, although patients with neuropathic pain are less likely to respond, there is a subset of patients that do gain pain relief without intolerable adverse effects.[21] Therefore, the diagnosis of neuropathic pain does not preclude opioid therapy. Although the inferred pathophysiology might suggest the likelihood of a response, opioid responsiveness cannot be reliably predicted in individual patients. Indeed, it has been suggested that opioid responsiveness represents a continuum with extensive overlap in the responsiveness of pain that is mediated by neuropathic, nociceptive and mixed pain mechanisms. A trial of opioid therapy will identify patients with chronic non-cancer pain who may gain substantial clinical benefit.[29] Further controlled clinical trials clearly are needed to better define the role of long-term opioid therapy in chronic non-cancer pain, and to establish criteria for patient selection and specific treatment algorithms.

4.2 Treatment Based on Pain Severity: the WHO Analgesic Ladder

A patient's report of pain is the most important factor in determining the degree of pain relief needed. The WHO has established a stepwise algorithm (the 'WHO Analgesic Ladder') for analgesic therapy for cancer pain based on severity.[30] Step 1 of the ladder recommends treatment for mild pain: paracetamol (acetaminophen), aspirin (acetylsalicylic acid) or other non-steroidal anti-inflammatory drugs (NSAIDs). If pain persists or increases, the addition of opioids, such as codeine, hydrocodone and oxycodone, is recommended as step 2. Step 2 opioids are frequently administered in fixed-dose combinations with paracetamol (acetaminophen) or aspirin. Step 3 opioids are prescribed when moderate-to-severe pain control is needed. Step 3 opioids include morphine, oxycodone, hydromorphone, methadone and fentanyl. Adjuvant agents may be added at any step to enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain and produce analgesic activity for specific types of pain.[31]

The WHO approach includes a framework for administering analgesics, which consists of the following five elements.

- By mouth: oral administration is effective, inexpensive and easy to titrate.
- By the clock: analgesics should be administered throughout the day using routine administration of immediate-release (IR) formulations or sustained-release (SR) preparations so that continuous pain relief is achieved.
- By the ladder: pain medication should be changed according to the severity of pain, as specified by the analgesic ladder.
- For the individual: because response to pain medication may differ, individualised treatment is required so that adequate pain relief is obtained for each patient.
- With attention to detail: patients must be closely monitored; pain assessment and frequent reassessment are cornerstones of effective pain management.

The WHO three-step analgesic ladder has been extensively validated in numerous studies and shown to be highly effective in managing cancer pain. For example, in a 10-year prospective study involving over 2 000 patients, 76% of patients reported good pain relief using analgesics prescribed according to the WHO guidelines, with a low rate of analgesia-associated complications.[32] In a second study involving 174 patients, oral drug therapy was successful in managing pain in 89% of patients. More than 80% described their pain as ranging between 'none' and 'moderate' when WHO guidelines were followed.[33]

The WHO ladder has been validated in patients with cancer pain, but it has not been validated in non-cancer settings. Several guidelines have recently been proposed for the use of opioids in chronic non-cancer pain.[21,34-36] These guidelines note the substantial personal and societal costs of chronic non-cancer pain and recognise that opioid therapy may provide benefits for some patients. Overall, these guidelines acknowledge that good medical practice should guide prescribing of opioids and that treatment should be tailored to the individual patient. Several suggest that opioids should be considered only after adequate trials of other alternative agents.[21] Common elements in these guidelines include: a thorough evaluation of the patient; generation of a clear treatment plan and objectives; a periodic review of treatment to assess safety, efficacy, compliance, misuse and to reassess pain; consultation or referral to other specialists in the case of comorbid psychiatric disorders or when there is a high index of suspicion for abuse; and detailed documentation of treatment (table II). However, empirical studies must yet be performed to substantiate these guidelines. Furthermore, minimal guidance is provided regarding the key issue of patient selection.[21]

The recent experience with prescription opioid drug abuse has heightened the need for good clinical judgement and increased attention to guideline recommendations. In a bulletin from the American Pain Society, it was stressed that 'opioids alone are rarely effective in the treatment of chronic pain. However, opioids can be effective in some patients as part of an interdisciplinary approach to diagnosis and treatment of chronic pain'. A balanced approach is now advocated, one that is able to address concerns of drug abuse and misuse, while preserving access for appropriate use.[37]

4.3 Route of Administration

The route of administration selected should be the safest and least invasive method that will provide effective analgesia.[18] For most patients, the oral route of administration is preferred because it is the most convenient, inexpensive and easy to titrate.[30,31] Other routes of administration are available if oral administration is not possible. For patients who cannot swallow or who have gastrointestinal obstruction, the rectal and transdermal routes provide alternatives that are less invasive than parenteral injection. Parenteral routes are preferred when patients require rapid onset of analgesia or need very high doses of opioids which cannot otherwise be conveniently administered.[18]

Table II. Common elements of guidelines for the use of opioids to treat patients with chronic non-cancer pain

Patient evaluation
Obtain a pain history and assess the impact of pain on social, occupational, physical and psychological function
Review previous diagnostic studies, other consultations and opinions, and previous surgical and medical interventions
Review medical, psychiatric and substance abuse history, and assess coexisting diseases or conditions
Conduct a directed physical examination
Treatment plan and objectives
Establish a working diagnosis and medical indication for treatment with opioids
Outline measurable outcome objectives (e.g., pain control, improvement in activities of daily living, functional improvement, sleep)
Provide informed consent on the risks and benefits associated with opioids
Need copy of informed consent
Discuss the conditions under which opioids will be prescribed and discontinued
Periodic review
Assess the safety and efficacy of treatment (e.g., subjective pain ratings, functional changes, quality of life, adverse effects, improvement in mood)
Assess for compliance and evidence of possible misuse (e.g., through use of screening tools, urine toxicology)
Reassess the nature of the pain complaint to confirm that opioid treatment is still warranted
Consultation
Referral to a specialist in pain medicine may be warranted depending on the level of prescribing comfort, expertise of the practitioner and the complexity of the problem
Referral to an addiction specialist is often indicated for patients with a history of addiction or substance use disorder
Referral to a psychiatrist or psychologist may be indicated for patients with significant psychiatric comorbidity
Documentation on the following areas should be maintained and updated on a regular basis
Evaluation
Diagnosis (including the reason for prescribing opioids if not obvious from the diagnosis)
All prescriptions
Overall plan to manage pain
Consultations received
Written instructions to the patient, the patient's consent and agreements with the patient

4.4 Dose Administration Regimens

Opioids should be administered around-the-clock for patients with chronic pain so that pain relief is continuous.[15,18] When this type of regimen is employed using a conventional IR formulation of morphine, however, administration every 3–4 hours is required. This may result in interruption of sleep, inconvenience to the patient, adverse effects leading to non-compliance and the potential for medical errors.[38] Over the past decade, several long-acting formulations have been developed for twice or once daily administration, including morphine-containing formulations with recommended dosage intervals of 8–12 hours (for a comprehensive listing of the trade names associated with morphine solutions, see *Martindale: The Complete Drug Reference*[39]). One oral morphine formulation is recommended for once daily administration (Kadian®/Kapanol®[1]).[40] The efficacy and safety of the once daily formulation has been directly compared with a formulation indicated for twice daily administration (MS Contin®) in a double-blind study in 152 patients with cancer pain.[38] The once daily and twice daily formulations provided similar pain control. The incidence of breakthrough pain, measured by the number of patients who required rescue medication, also was comparable between the two formulations. There were no significant differences between the formulations in the frequency or severity of adverse events. Pa-

1 Use of trade names is for product identification purposes only and does not imply endorsement.

tient global assessment of pain control significantly favoured the once daily formulation.[38]

Oxycodone is available in a SR formulation indicated for twice daily administration. The efficacy of this formulation in the treatment of chronic cancer pain has been compared with IR oxycodone in a multicentre, randomised, double-blind, parallel-group study in 111 patients.[41] Patients were treated with IR oxycodone 15mg four times daily or SR oxycodone 30mg every 12 hours for 5 days. The 5-day mean pain intensity scores were 1.1 ± 0.1 for the IR preparation and 1.4 ± 0.1 for the SR preparation. Furthermore, adverse events and discontinuation rates for the two treated groups were similar, indicating that patients can be equally well treated whether they are administered IR or SR oxycodone.[41]

Fentanyl is available in a transdermal formulation. The usual dosage interval is 72 hours, although some patients require a dosage interval of 48 hours to maintain adequate analgesia.[18,42] The efficacy of transdermal fentanyl and a twice daily oral SR morphine preparation (MS Contin®) were compared in 202 patients with cancer in a randomised, open, two-period, crossover study. Both treatments were equally effective for pain control as assessed by the Memorial Pain Assessment Card and European Organisation for Research and Treatment of Cancer (EORTC) pain scores. Regarding adverse effects, fentanyl was associated with significantly less constipation and daytime drowsiness, but greater sleep disturbance and shorter sleep duration than the morphine formulation.[43] In a recent study, quality of life assessment and patient preference favoured transdermal fentanyl.[44]

All patients with cancer who receive an around-the-clock regimen should be supplied with rescue medication to be used on an as-needed basis should breakthrough pain occur. A limited supply of a short-acting rescue medication should also be made available for patients with chronic non-cancer pain.

4.5 Dosage Initiation and Titration

Treatment in opioid-naïve patients is often initiated using a conventional formulation. Recommended starting doses and schedules are provided in table III. Opioids with short half-lives such as morphine, hydromorphone, fentanyl or oxycodone are preferred because they are easy to titrate. Titration is necessary to establish the optimal balance between analgesia and adverse effects; titration starting with low doses also is necessary to avoid severe adverse effects. The rate of titration should be guided by the patient's report of pain intensity.[18]

Table III. Dose administration data for opioid analgesics in patients with moderate to severe chronic pain[15]

Drug	Approximate equianalgesic oral dose	Approximate equianalgesic parenteral dose	Recommended starting dose (adults >50kg bodyweight)	
			Oral	Parenteral
Morphine	20–60mg/day initial starting dose; then 30mg q3–4h (IR)	10mg q3–4h	30mg q3–4h[a]	10mg q3–4h (use of IV route is preferable)
Fentanyl		0.1[b]		
Oxycodone	30mg q3–4h (IR)	NA	10mg q3–4h	NA
Hydromorphone[c]	7.5mg q3–4h	1.5mg q3–4h	6mg q3–4h	1.5mg q3–4h
Methadone	5–10mg q6–8h	5–10mg q6–8h	5–10mg q6–8h	2.5–5mg q6–8h

a Starting dose of 20 to 60mg/day may be used to avoid adverse effects such as vomiting.

b Transdermal fentanyl 100 µg/hr is approximately equivalent to 2–4 mg/hr of IV morphine. A conversion factor for transdermal fentanyl that can be used for equianalegesic calculation is 17 µg/hr. Roughly, the dose of transdermal fentanyl in µg/hr is approximately one-half of the 24-hour dose of oral morphine.[45]

c For morphine and hydromorphone, rectal administration is an alternate route for patients unable to take oral medication, but equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

IR = immediate release; **IV** = intravenous; **NA** = not available; **qXh** = every X hours.

Under certain circumstances, it is necessary to switch to an alternative opioid. For instance, a patient may experience dose-limiting adverse effects without achieving adequate pain control. An equianalgesic dose table should be used to determine the starting dose of the new drug (table III). When switching to a different opioid, it is recommended that only one-third to one-half of the calculated equianalgesic dose should be administered initially.[45]

4.6 Adverse Effects of Opioid Therapy

4.6.1 Constipation

Constipation is a common adverse effect of long-term opioid therapy.[18,31] Because it is so common, laxative medications should be used concurrently in most patients. Mild constipation may be managed with increased fibre consumption and mild laxatives. Severe constipation can be treated with stimulating cathartic drugs such as bisacodyl, senna or phenolphthalein. Stool softeners in combination with a stimulant laxative also may be helpful.[18,31]

4.6.2 Nausea and Vomiting

Nausea and vomiting are common upon initiation of opioid therapy, occurring in approximately 30–60% of patients.[46,47] A majority of patients will habituate to nausea and vomiting over the first week of treatment. Three mechanisms are responsible for these adverse effects: opioid activation of a chemoreceptor trigger zone for emesis, reduced gastrointestinal motility, or increased vestibular sensitivity.[48]

Treatment consists of concurrent use of antiemetic agents, which include metoclopramide, antihistamines, haloperidol, chlorpromazine, prochlorperazine, scopolamine, or 5-HT_3 receptor antagonists (ondansetron, tropisetron). Metoclopramide is generally recommended as first-line therapy because it improves gastrointestinal motility and acts at the chemoreceptor trigger zone. Antihistamines may be used in patients when vestibular sensitivity is suspected or in the case of bowel obstruction. Haloperidol also may be used in patients with bowel obstruction. Chlorpromazine, an agent with modest antiemetic activity, is another option, although it is associated with a high incidence of sedation, postural hypotension, and anticholinergic adverse events. Prochlorperazine is a stronger antiemetic but causes greater extrapyramidal effects. Scopolamine may be used, but this agent often is limited by anticholinergic side effects. The role of the 5-HT_3 receptor antagonists in patients with opioid-induced emesis remains to be better established.[48]

4.6.3 Sedation and Cognitive Impairment

Somnolence or cognitive impairment may occur when opioid administration is initiated or during significant dose escalation. It is generally transitory, as tolerance usually develops rapidly.[31] Several research groups have sought to assess the impact of long-term opioid use on psychomotor performance using measures of driving ability.[49,50] In one study, psychological and neurological tests originally designed for professional motor vehicle drivers were conducted in 24 patients on continuous morphine for cancer pain and 25 patients with cancer who were pain-free and did not require analgesia. Although results were slightly worse in patients taking morphine, there were significant between-group differences in only one measure. The authors concluded that long-term morphine treatment had only a slight and selective effect on functions related to driving.[50] Galski and colleagues used several off-road tests, including pre-driver evaluation (PDE), a simulator evaluation (SDE), and behavioural observation during simulator performance to assess driving ability in a small pilot study involving 16 patients with chronic non-cancer pain who were being treated with long-term opioid therapy.[49] These 16 patients were compared with a historical control group of cerebrally compromised patients who had taken similar tests as well as an on-road test. Patients who were receiving long-term opioid therapy generally performed better than the historical controls. While the results of this small pilot study remain to be confirmed, it suggested that long-term opioid therapy did not significantly impair perception, cognition, coordination and behaviour

measured in off-road tests.[49] However, it must be noted that the issue of driving ability in patients receiving long-term opioid treatment for chronic pain is an important one that requires further clinical research.

4.6.4 Respiratory Depression

Respiratory depression is the most dangerous adverse effect of opioid therapy. However, respiratory depression is rare when the opioid dose is carefully titrated[18] and patients receiving long-term opioid therapy usually develop tolerance to respiratory-depressant effects.[31] Physical stimulation of a symptomatic patient may be enough to prevent significant hypoventilation. Because of the risk of withdrawal syndrome and return of pain in patients who are receiving opioids on a long-term basis, opioid antagonists should be used with caution.[31]

4.6.5 Tolerance and Physical Dependence

Tolerance to the pain-relieving effects of opioids describes the need to increase the dose over an extended period of time to maintain pain relief. Patients also develop tolerance to the adverse effects of an opioid, the exception being constipation.[31] Physical dependence manifests as a withdrawal syndrome when dosage is abruptly reduced or an opioid antagonist is administered.[18] Symptoms of physical dependence can also manifest after tapering the dose gradually and, particularly, after stopping the opioid. Typical signs are anxiety, irritability, chills and hot flashes, joint pain, lacrimation, rhinorrhoea, diaphoresis, sleep disturbances, nausea, vomiting, and abdominal cramps and diarrhoea.[31] It is not a manifestation of addiction nor is it a clinical problem if patients are warned not to abruptly discontinue drug therapy. If treatment discontinuation is indicated, the withdrawal syndrome can generally be avoided using a tapering regimen.[18]

Physical dependence and addiction are not interchangeable terms. Addiction is psychological dependence on the use of substances for their psychic effects. It is characterised by a core group of aberrant drug-related behaviours, including loss of control over drug use, compulsive drug use and continued use despite harm.[20] Selling prescription drugs, prescription forgery, stealing drugs from others and obtaining prescription drugs from non-medical sources are clear indicators of addiction and/or abuse. On the other hand, less overt behaviours, such as aggressive complaining about the need for more drugs or drug hoarding during periods of reduced symptoms, may be more difficult to assess.[20] Other signs of concern include repeated lost prescriptions, multiple requests for early refills and a desire to continue excessive use of short-acting opioids. If there are multiple episodes of less obvious behaviours, further assessments may be necessary. Increased attention to the issue of addiction and problematic prescription opioid use has led to the development of specific screening tools to assess addictive disease in patients with chronic pain, agreements for patients that clearly specify conditions for opioid treatment and urine toxicology to monitor use.[36,51,52]

Clinicians should be alert to the signs of addiction, particularly when treating patients with existing alcoholism or drug abuse/addiction history. It is important to note that exposure of patients to opioids does not necessarily cause addiction. Rates of drug abuse and addiction in patients with chronic non-cancer pain have been estimated to be between 3.2 and 18.9%.[21] A recent retrospective survey of medical records assessed the medical use of commonly used opioid agents in relationship to hospital emergency department admissions resulting from drug abuse.[53] Between 1990 and 1996, the medical use of morphine, fentanyl, oxycodone and hydromorphone to treat pain increased substantially. Over the same period, reports of opioid abuse relative to total drug abuse decreased from 5.1 to 3.8%. Therefore, the trend of increasing medical use of opioids was not associated with proportional increases in opioid abuse. The results of this survey address an important barrier to effective pain management by overturning the notion that increased medical use of opioids leads to abuse.[53]

5. Opioids for Treating Chronic Pain

Commonly available opioid agents are described in this section. All of these agents are strong opioids and full agonist drugs. They are discussed here based on their formulation, and are subdivided into short-acting opioids, opioids with an intermediate duration of action, long-acting opioids, and those with actions of a variable length. New formulations and delivery systems are responsible for the decreased dose administration intervals and greater convenience afforded by longer-acting preparations.

5.1 Short-Acting Opioids

5.1.1 Morphine

IR morphine is the most widely used opioid and the standard against which new agents are measured.[15] By convention, the relative potency of commonly used opioids is based upon a comparison with 10mg parenteral morphine.[18] The elimination half-life of IR morphine in patients with normal renal function is 2 hours, and the duration of action is 3–6 hours. IR morphine is available in a wide variety of preparations, including oral capsules, solution and tablets; parenteral injection for intramuscular, intravenous, subcutaneous, epidural and intrathecal use; and by rectal suppository.

5.1.2 Oxycodone

Oxycodone, combined with paracetamol (acetaminophen) or aspirin, is a step 2 analgesic used to control moderate pain. As a single agent, it is used to manage severe pain.[18] It has a higher oral bioavailability than morphine and comparable analgesic potency.[18] The half-life after single-dose administration of oral oxycodone has been shown to be approximately 3.5 hours,[54] although others have found a slower elimination half-life in the range of 5 hours.[55] These differences may in part be explained by individual variations in metabolism, highlighting the need for careful monitoring during the initial titration phase.

5.1.3 Hydromorphone

Hydromorphone has an elimination half-life of 2–3 hours and a duration of action of 2–4 hours.[18] It is available in a variety of formulations for oral, parenteral and rectal administration. Because of its high solubility, it can be prepared at a high concentration for parenteral injection. It therefore can be used in patients who require large doses of opioids for adequate pain relief and it is commonly used for continuous subcutaneous infusion.[18,56]

5.2 Opioids with an Intermediate Duration of Action

5.2.1 Morphine

Several SR morphine preparations are available for twice-daily administration (eg, MS Contin®, Oramorph SR®). It is important to note that the pharmacokinetic profiles of twice-daily formulations are quite different from IR preparations. An IR dose of morphine reaches a peak plasma concentration within the first hour and has an elimination half-life of 2–4 hours. Twice-daily formulations have an approximate 3- to 6-hour elimination half-life, the peak is attenuated in comparison to IR formulations and the plasma concentrations are sustained over a 12-hour period.[18] The recommended dosage interval is every 12 hours, although the dose administration regimen should be adjusted on the basis of individual patient needs.[57]

5.2.2 Oxycodone

An SR oxycodone formulation for twice-daily administration is available (Oxycontin®). It displays a biphasic pharmacokinetic profile, with an initial half time of absorption of 0.6 hours and a second half time of absorption of 6.9 hours. This represents an initial release of oxycodone from the tablet, followed by a prolonged release. The half-life of elimination of SR oxycodone is 4.5 hours.[58]

Although package inserts for SR oxycodone suggest an equivalency ratio of 2 : 1 for oral morphine to oral oxycodone, others recommend a milligram-to-milligram conversion (1 : 1) in the opioid-tolerant patient. Ratios of 1 : 1 and 1.3 : 1

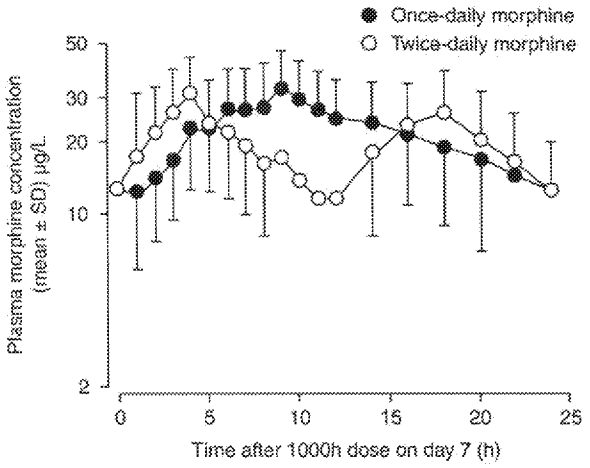

Fig. 1. Mean (±SD) plasma morphine concentration as a function of time at steady state for a once-daily morphine formulation (Kadian®/Kapanol®, closed circles) and a twice-daily morphine formulation (MS Contin®, open circles) [reproduced with permission from Gourlay[40]].

(oral oxycodone to oral morphine) have been found to be effective and safely used in chronic cancer pain.[44]

5.3 Long-Acting Opioids

5.3.1 Once-Daily Morphine

One oral morphine formulation is recommended for once-daily administration (Kadian®/Kapanol®).[40] In contrast to SR morphine for twice-daily administration, the once-daily SR morphine preparation has an elimination half-life of approximately 10 hours.[40] As noted earlier, the safety and efficacy of once daily administration has been established.[38] Figure 1 shows the mean plasma concentrations of morphine as a function of time at steady state for the once-daily formulation administered every 24 hours and a twice-daily morphine formulation (MS Contin®) administered every 12 hours.[59] The once-daily formulation demonstrated a less variable pharmacokinetic profile compared with the twice-daily formulation even though the dose administration interval for the once-daily formulation was twice that of the twice-daily formulation.[59] Both formulations provided excellent pain control.[40]

The once-daily formulation also is effective and can be safely used for twice-daily administration.[38] Figure 2 shows plasma morphine concentrations at steady state following administration of an IR morphine solution every 4 hours, and a twice-daily and a once-daily formulation administered every 12 hours.[60] Comparison with the once-daily formulation, the twice-daily formulation released proportionally more morphine in the first 4-hour time interval, equivalent amounts between 4–8 hours, and significantly less morphine in the 8- to 12-hour time interval. These results are consistent with clinical experience, which indicates that the twice-a-day formulation, in a percentage of patients, requires administration every 8 hours. In contrast, the relatively flat plasma morphine concentration-time profile for the once-daily formulation indicates that it can be administered at 12-hour intervals.[60]

5.3.2 Transdermal Fentanyl

Fentanyl is a semisynthetic opioid that is approximately 100 times more potent than morphine.[15] Fentanyl, available in a transdermal for-

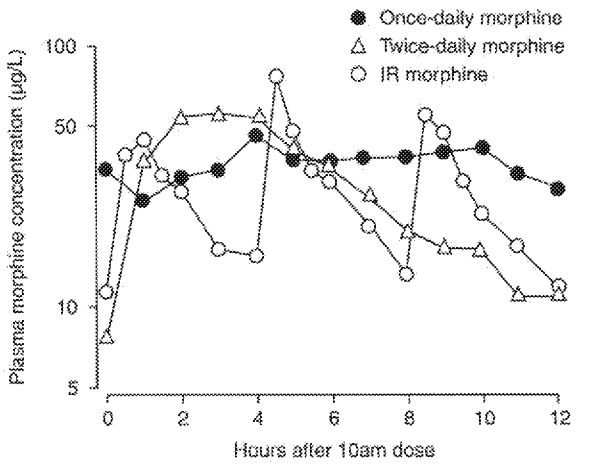

Fig. 2. Plasma morphine concentrations in a representative patient as a function of time at steady state following the administration of the same morphine dose (120mg/24h). A long-acting morphine formulation (Kadian®/Kapanol®, closed circles) and a twice-daily formulation (MS Contin®, open triangles) were administered twice daily. Immediate-release (IR) morphine solution (open circles) was administered every 4 hours (reproduced with permission from Gourlay[60]).

Table IV. Barriers to cancer pain management

Problems related to healthcare professionals	Inadequate knowledge of pain management	
	Poor assessment of pain	
	Concern about regulation of controlled substances	
	Fear of patient addiction	
	Concern about adverse effects of analgesia	
	Concern about patients becoming tolerant to analgesics	
Problems related to patients	Reluctance to report pain	Concern about distracting physicians from treatment of underlying disease
		Fear that pain means disease is worse
		Concern about not being a 'good' patient
	Reluctance to take pain medication	Fear of addiction or of being thought of as an addict
		Worries about unmanageable adverse effects
		Concern about becoming tolerant to pain medications
Problems related to the healthcare system	Low priority given specifically to cancer pain treatment	Inadequate reimbursement
		The most appropriate treatment may not be reimbursed or may be too costly for families
	Restrictive regulation of controlled substances	
	Problems of availability of or access to treatment	

mulation, is released from the transdermal reservoir at a nearly constant rate; serum concentrations increase gradually after application, level off at 12–24 hours and then decline gradually.[18] When the patch is removed, the mean apparent half-life is approximately 17 hours (range: 13–22 hours). There is significant interindividual variability in fentanyl bioavailability.[18,42] One limitation to its use is poor adhesion to the skin of some patients.[18]

5.4 Opioids with a Variable Duration of Action

5.4.1 Methadone

Methadone is used to control pain, and to treat opioid abstinence syndromes and heroin users.[15] It has a higher oral bioavailability than morphine, a comparable duration of action of 4–8 hours and a much longer elimination half-life of 15–48 hours.[18] Methadone has non-competitive antagonistic activity at N-methyl-D-aspartate (NMDA) receptors, which suggests that it may have clinical utility in treating patients with neuropathic pain.[61] Methadone is a difficult drug to titrate because of its variable half-life and because plasma concentrations tend to rise with repeated dose administration. Methadone and morphine have been shown to be equipotent in single-dose studies but methadone is several times more potent than morphine with repeated administration.[18] This enables either lower dosage or longer dosage intervals. Both oral and parenteral routes are available; the subcutaneous route is not recommended because it causes local skin irritation.[18] An advantage to the use of methadone is that it is relatively inexpensive.

6. Challenges in Chronic Pain Management

Despite published guidelines for pain management, patients experiencing chronic pain – even chronic cancer pain – may not receive adequate analgesia. Cleeland and colleagues surveyed 1 308 outpatients with metastatic cancer, of whom 65% had reported pain or had taken analgesic drugs daily during the week preceding the study. Over one-third of patients described their pain as severe enough to impair their ability to function. Among these patients, 42% of patients with pain were not given adequate analgesic therapy, as assessed by guidelines developed by the WHO.[62] Important barriers to pain management still exist. Jacox et al. found barriers to pain management in the AHCPR cancer pain management guidelines related to healthcare professionals, patients and the healthcare system itself (table IV).[31]

While there is no 'perfect' opioid analgesic that is capable of providing complete pain relief in all patients without any negative consequences, successful pain relief without intolerable adverse effects is an attainable goal for many patients with chronic pain.

The recognition that disabling pain is still under-recognised and under-treated has led to the development of standards that are explicit about the need for improved pain assessment and management. For example, the JCAHO recently developed evidence-based standards for pain assessment that call for healthcare organisations to:

- recognise patients' rights to pain control
- screen for pain
- perform a complete assessment when pain is present
- record the assessment in a way that facilitates regular reassessment and follow-up
- set a standard for monitoring and intervention
- educate providers and assure staff competency
- establish policies that support appropriate prescription or ordering of pain medicines
- educate patients and families
- include pain needs for symptom control in discharge planning and
- collect data to monitor the effectiveness and appropriateness of pain management.

The JCAHO pain management standards are a formal mandate to incorporate principles of pain management into the patterns of daily medical practice in order to address institutional barriers to adequate pain control.

7. Conclusions

It is essential that all clinicians who treat patients with chronic pain recognise that it is their responsibility to provide effective pain management. In order to do so, physicians must be knowledgeable in general principles of pain management, analgesic pharmacology, special issues related to opioid therapy and the use of commonly available agents. Opioid analgesics are the standard of care for patients with moderate-to-severe chronic cancer pain. How opioids should be used in patients with chronic non-cancer pain is still a matter of debate. Further controlled clinical trials are needed to better define the role of long-term opioid therapy in patients with chronic non-cancer pain, and to establish criteria for patient selection and specific treatment algorithms. Given the large personal and socioeconomic burdens of chronic non-cancer pain, there is an increasing consensus of opinion that opioid treatment should be considered in selected patients after reasonable trials of other agents have failed. In addition, it is recognised that careful attention must be paid to treating the whole patient and not just the pain. A balanced, multidisciplinary approach that takes into account the individual needs of each patient is advocated. The ultimate imperative for all clinicians is to relieve unnecessary pain.

Acknowledgements

Dr Nicholson has no conflicts of interest directly relevant to the contents of this manuscript but is a consultant and a member of the speakers bureau for Pfizer Inc., Novartis Pharmaceuticals Corporation, Élan Pharmaceutical, Faulding, and Ortho-McNeil, and is a consultant for Medtronic.

References

1. Sriwatanakul K, Weis OF, Alloza JL, et al. Analysis of narcotic analgesic usage in the treatment of postoperative pain. JAMA 1983; 250: 926-9
2. Donovan M, Dillon P, McGuire L. Incidence and characteristics of pain in a sample of medical-surgical inpatients. Pain 1987; 30: 69-78
3. Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer 1982; 50: 1913-8
4. Grossman SA, Sheidler VR, Swedeen K, et al. Correlation of patient and caregiver ratings of cancer pain. J Pain Symptom Manage 1991; 6: 53-7
5. Miaskowski C. Effective cancer pain management: from guidelines to quality improvement. Seattle (WA): International Association for the Study of Pain. 1994
6. Merskey H, Bogduk N, editors. Classification of chronic pain. 2nd ed. Seattle: IASP Press, 1994: 209-14
7. Payne R. Chronic pain: challenges in the assessment and management of cancer pain. J Pain Symptom Manage 2000; 19: S12-5
8. Bonica J. General considerations of chronic pain. In: Bonica J, editor. The management of pain. Vol. 1. Philadelphia (PA): Lea and Febiger, 1990: 180-3
9. Siddall PJ, Cousins MJ. Spinal pain mechanisms. Spine 1997; 22: 98-104
10. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999; 353: 1959-64